The Selective Claisen and Dieckmann Ester Condensations Promoted by Dichlorobis(trifluoromethanesulfonato)titanium(IV)

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Inter and intramolecular condensations (the Claisen and the Dieckmann condensations) between ester functions have been performed by the combined use of dichlorobis(trifluoromethanesulfonato)titanium(IV) (= dichlorobis(triflato)titanium(IV)) and tertiary amine under mild reaction conditions. These results led to the development of the selective (crossed) Claisen and Dieckmann ester condensation between methoxymethyl ester and methyl ester, in that, dichlorobis(triflato)titanium(IV) contribute to control the direction of the reaction.

The Claisen and the Dieckmann ester condensations are the most fundamental and useful carbon-carbon bond forming reactions in organic synthesis.[1] However, the utility of these reactions have been limited by the several problems. Basic labile functional groups could be hardly introduced in the substrates employed, because these reactions are conventionally carried out in basic media. And, it is more of critical that it has been difficult in controlling the direction of the reaction, namely when the condensation is carried out between two different esters, each of which possesses α-hydrogen, a mixture of all four products is generally obtained.[2] To evade the problem, esters lacking α-hydrogen such as benzoates, carbonates, and oxalates are commonly employed as acylating agents.

In the preceding communications,[3] we have reported the Claisen and the Dieckmann ester condensation between alkyl esters and the crossed type of the ester condensation between methoxymethyl ester and methyl ester could be performed under mild reaction conditions by using dichlorobis(trifluoromethanesulfonato)titanium(IV)[4] (=dichlorobis(triflato)titanium(IV)). In this paper, the author describe the results of the studies on them in detail.
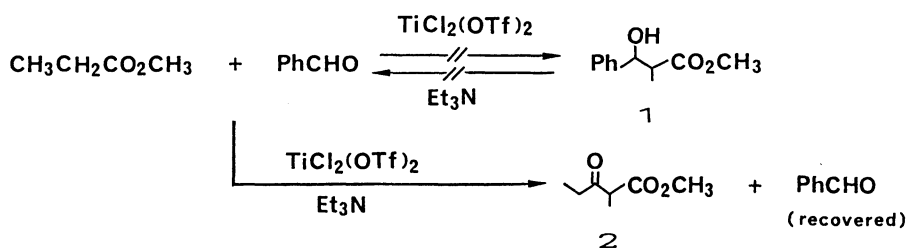
Results and Discussion

The characteristic properties of the metal triflates (trifluoromethanesulfonates) system had led to the development of significant carbon–carbon bond forming reactions in organic synthesis.[5] In particular, dialkylboryl triflates and tin(II) triflates mediated synthetic processes enjoyed highly regio-, stereo-controlled aldol type[5a-f] and the Michael type[5g,h] reactions.

In connection with the progress, we paid our attention to the utilization of titanium(IV) triflates species, which were known in inorganic chemistry.[4,6] Among the four feasible titanium(IV) spesies, we chose the most stable and accessible dichlorobis(trifluoromethanesulfonato)titanium(IV) (=dichlorobis(triflato)titanium(IV)).[7]

Firstly, we studied the ability of dichlorobis(triflato)titanium(IV) ($TiCl_2(OTf)_2$) to generate the enolate from ester, because tin(II) triflate or dialkylbolyl triflate fail to promote the reaction perhaps due to the low acidity of α-proton of ester. The addition reaction of methyl propionate with benzaldehyde in the presence of $TiCl_2(OTf)_2$ and triethylamine (molar ratio of ester:aldehyde:$TiCl_2(OTf)_2$:Et₃N=1.0:1.1:1.1:1.1) was found to give not even a trace amount of the β-hydroxy ester **1**, but unexpectedly methyl 2-methyl-3-oxovalerate (**2**) as a main product in 36% yield. Meanwhile, treatment of the β-hydroxy ester **1** with $TiCl_2(OTf)_2$ and triethylamine under the same conditions did not take place the retro-aldol reaction and the ester **1** was recoverd quantitatively. The crossover experiment showed that the aldol-type reaction did not occured at all in this system (Scheme 1).

Based on these results, the different type of Claisen ester condensation under nonbasic media were studied. To optimize the conditions, intramolecular cyclization (the Dieckmann condensation) of dimethyl adipate was examined. Among several solvents screened, dichloromethane gave the best result in yield (Table 1). Tertiary amines such as triethylamine or *N,N*-diisopropylethylamine was found to give good results. As molar ratio, the combined use of 1.5 equivalent of $TiCl_2(OTf)_2$ and 2.2 equivalent of triethylamine gave

Scheme 1.

Table 1. Effect of the Solvent on the Dieckmann Condensation of Dimethyl Adipate[a]

$$\text{CO}_2\text{CH}_3 \qquad \xrightarrow[\text{amine}]{\text{TiCl}_2(\text{OTf})_2} \qquad \text{CO}_2\text{CH}_3$$

Solvent	Yield of 2-methoxycarbonyl-1-cyclopentanone/%	Recovery of dimethyl adipate/%
Toluene	32	55
Tetrahydrofuran[b]	0	—
Ether	17	75
Dichloromethane	55	42
1,2-Dichloroethane	35	55

a) The reaction was carried out at 0 °C for 2 h employing triethylamine as base. Molar ratio of dimethyl adipate: $\text{TiCl}_2(\text{OTf})_2$: $\text{Et}_3\text{N}=1.0:1.1:1.5$. b) Tetrahydrofuran was polymerized in this condition.

Table 2. Effect of Bases and Molar Ratio on the Dieckmann Condensation of Dimethyl Adipate[a]

Entry	Base(equiv)		Equiv of $\text{TiCl}_2(\text{OTf})_2$	Yield/%[b]
1	Pyridine	(2.2)	1.1	5>
2	Cesium Fluoride	(2.2)	1.1	0
3	N-Ethylpiperidine	(2.2)	1.1	30
4	Diisopropylethylamine	(2.2)	1.1	45
5	DBU	(2.2)	1.1	0
6	2,6-Lutidine	(2.2)	1.1	10
7	Triethylamine	(1.1)	1.1	35
8	Triethylamine	(2.2)	1.1	55
9	Triethylamine	(2.2)	1.5	71
10	Triethylamine	(3.3)	1.1	38
11	Triethylamine	(3.3)	1.5	48
12	Triethylamine[c]	(2.2)	1.5	80

a) The reaction was carried out at 0 °C for 2 h employing dimethyl adipate as substrate. b) Isolated yield. c) In the presence of Molecular Sieves 4A.

the best yield (Table 2). The tendency of these conditions is similar to those of other metal (tin(II) and boryl) triflates systems. A somewhat excess of $\text{TiCl}_2(\text{OTf})_2$ was required to complete the reaction perhaps owing to compensate the reagent decomposed by an equimolar amount of methanol produced during the condensation. The addition of Molecular Sieves 4A to catch the methanol slightly effected the yield.

Analogous types of titanium complexes such as dichlorobis(fluorosulfonato)titanium(IV) $(\text{TiCl}_2(\text{SO}_3\text{F})_2)$,[8] titanium(IV) chloride (TiCl_4), and bis(η-cyclopentadienyl)bis(trifluoromethanesulfonato)titanium(IV) $(\text{Ti-Cp}_2(\text{OTf})_2)$[9] were also applied to expect the same reaction. However, their titanium(IV) reagents failed to proceed the condensation reaction, probably because $\text{TiCl}_2(\text{SO}_3\text{F})_2$ could be hardly soluble in dichloromethane during the reaction and TiCl_4, $\text{TiCp}_2(\text{OTf})_2$ are less reactive compared with $\text{TiCl}_2(\text{OTf})_2$ as Lewis acid.

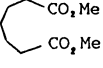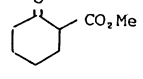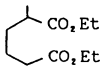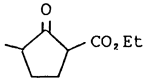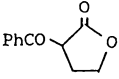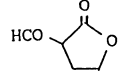Methyl 5-(chloroformyl)valerate was examined as substrate to compare the reactivity with dimethyl adi-pate, but no reaction occured at all under the same conditions. The results suggest that the capture of the methoxyl group by $\text{TiCl}_2(\text{OTf})_2$ correlates the driving force of the reaction.

Several examples of the condensation under the optimum conditions were depicted in Table 3. α-unsubstituted esters could be subjected to self ester condensation (Entries 1—3), whereas no desired compound was obtained in the case of α-alkyl-substituted ester such as methyl isobutyrate (Entry 5). The result reflected on the regioselective cyclization of diethyl 2-methyladipate to afford only 2-ethoxycarbonyl-5-methylcyclopentanone (Entry 6). Benzoylation, formylation, and oxalylation were similarly performed employing third fold excess of the corresponding acylating reactants (Entries 7—11).
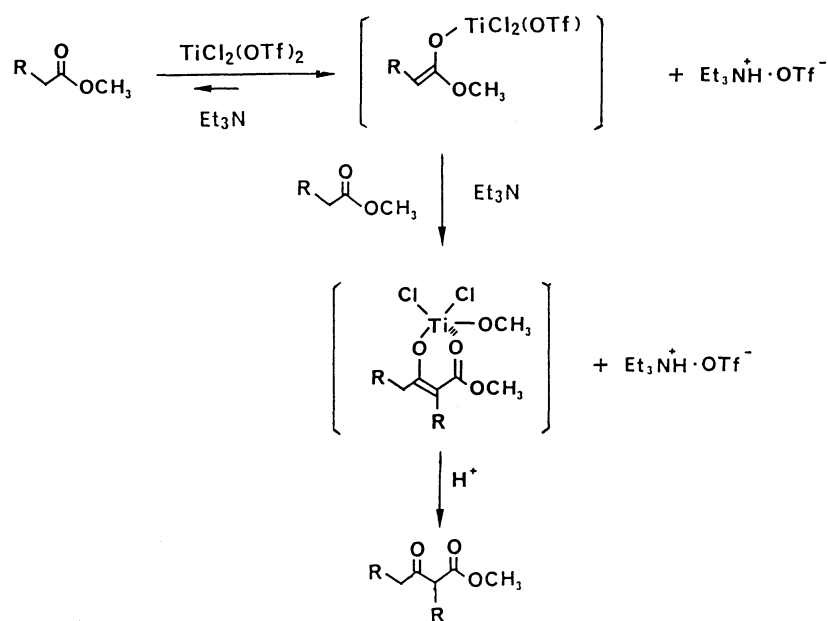
A plausible mechanism is illustrated in Scheme 2. Small amount of the enolate of an ester in the system, which is successively generated from the ester on equilibrium, immediatly transformed into more stable titanium salt of the enol of the corresponding β-keto ester. The resultant titanium salt of the β-keto ester is quenched by water to give the product. This speculation could be supported by the following facts; (1) the aldol-type reaction did not proceeded under this condition, (2) also in the usual Claisen condensation α-alkyl-substituted ester required more harsh basic conditions.[1a]

In due consideration of the dichlorobis(triflato)titanium(IV) promoted Claisen ester condensation, we studied the direct and the crossed (regiocontrolled) type-Claisen ester condensation which was hitherto enable to be realized under commonly known basic conditions.[10,11] To answer the problem, we planned regioselective enolate formation of one of the two different ester functions. In the hope that titanium(IV) species exhibit the strong chelating ability toward oxygen or sulfur atom adjacent to ester functions, methoxymethyl ester 13, methylthiomethyl ester 14, and 2-methoxyethyl ester 15 were examined to produce the enolate predominantly against methyl ester through intramolecular (the Dieckmann) condensa-

Table 3.   Several Types of Ester Condensation^a)

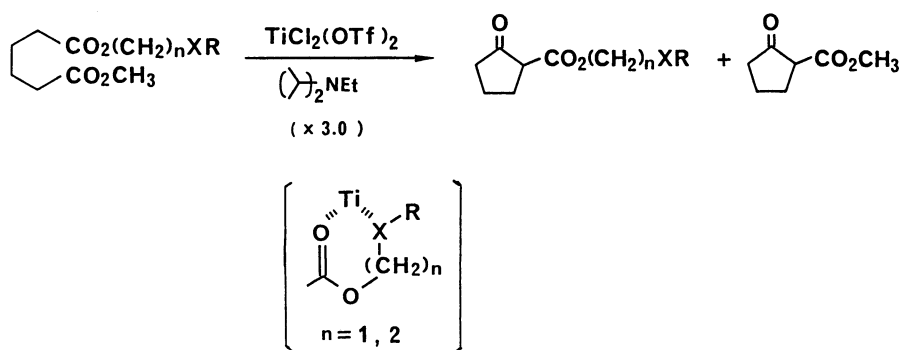| Entry	Ester(substrate)	Acylating reagent^b)	Conditions	Yield/%^c)	Product	
1	$CH_3CH_2CO_2Me$	—	0 °C, 2 h	72	$EtCOCH(CH_3)CO_2Me$	3
2	$CH_3CH_2CO_2Et$	—	0 °C, 2 h	70	$EtCOCH(CH_3)CO_2Et$	4
3	$PhCH_2CH_2CO_2Me$	—	0 °C—r.t.,10 h	55	$PhCH_2CHCO_2Me$ / $COCH_2CH_2Ph$	5
4	(cyclohexane-1,2-dicarboxylate, CO_2Me / CO_2Me)	—	0 °C—r.t.,10 h	51	(2-oxocyclohexane, CO_2Me)	6
5	$i\text{-}PrCO_2Me$	—	0 °C—r.t.,10 h	0	—	
6	(structure, CO_2Et / CO_2Et)	—	0 °C—r.t.,10 h	56	(cyclopentanone, CO_2Et)	7
7	$PhCH_2CH_2CO_2Me$	$PhCO_2Me$	0 °C—r.t.,10 h	71	$PhCH_2CHCO_2Me$ / $COPh$	8
8	$PhCH_2CH_2CO_2Me$	HCO_2Et	0 °C—r.t.,10 h	59	$PhCH_2CHCO_2Me$ / CHO	9
9	$PhCH_2CH_2CO_2Me$	$HCOCO_2Et$	0 °C—r.t.,10 h	62	$PhCH_2CHCO_2Me$ / $COCHO$	10
10	γ-Butyrolactone	$PhCO_2Me$	0 °C—r.t.,10 h	70	(butyrolactone, $PhCO$)	11
11	γ-Butyrolactone	HCO_2Et	0 °C—r.t.,10 h	52	(butyrolactone, HCO)	12

a) The reaction was carried out in CH_2Cl_2 in the presence of M.S. 4A. Molar ratio of $TiCl_2(OTf)_2$: Et_3N : ester (substrate)=1.5:2.2:1.0. b) Three equiv of acylating reagents vs. esters (substates) were used. c) Isolated yield.

Scheme 2.

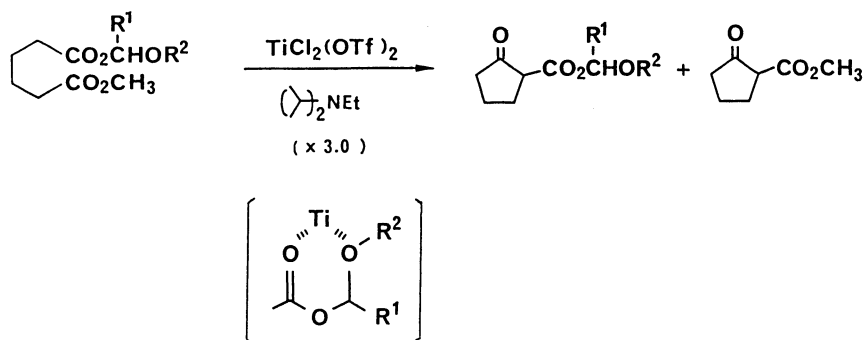tion as depicted in Scheme 3.[12] Among them, methoxymethyl methyl adipate (13) was found the appropriate substrate: methoxymethyl 2-oxocyclo-pentanecarboxylate (16), the desired β-keto ester was obtaied as the main product along with a trace amount (<3%) of 2-(methoxycarbonyl)cyclopentanone. Other alkoxymethyl esters such as isopropoxymethyl methyl adipate (19), benzyloxymethyl methyl adipate (20), 1-

Scheme 3.

Scheme 4.

Table 4. Condensation of Methoxymethyl Methyl Adipate (13)[a]

Entry	Aminine (equiv) vs. 13	Conditions	Yield of 16/%	Recovery of 13/%
1	Triethylamine (3.0)	0 °C, 1h	31	52
2	Triethylamine (3.0)	−23 °C, 1h	45	41
3	N,N-Diisopropylethylamine (2.0)	−23 °C, 1h	69	22
4	N,N-Diisopropylethylamine (3.0)	−23 °C, 1h	83	3
5	N,N-Diisopropylethylamine (3.5)	−23 °C, 1h	82	0
6	Tributylamine (3.0)	−23 °C, 1h	62	18
7	N-Methylpiperidine (3.0)	−23 °C, 1h	71	7
8	N-Ethylpiperidine (3.0)	−23 °C, 1h	77	5
9	N-Ethylpiperidine (3.0)	−23 °C, 3h	83	5

a) The reaction was carried out in dichloromethane and the molar ratio of TiCl$_2$(OTf)$_2$: 13=1.3 : 1.0. 2-Methoxycarbonyl-1-cyclopentanone was produced with only a trace amount in every conditions.

Table 5. Self Condensation of Methyl
3-Phenylpropionate[a]

$$Ph\text{—}CO_2CH_3 \xrightarrow[\substack{(\text{—})_2NEt}]{TiCl_2(OTf)_2} Ph\text{—}\overset{O}{\underset{Ph}{C}}\text{—}\overset{O}{C}\text{—}OCH_3$$

5

Entry	Conditions	Yield of 5/%
1	0 °C—r.t., 10 h	37
2	0 °C, 3h	15
3	−23 °C, 3h	trace

a) The reaction was carried out in CH_2Cl_2 and the molar ratio of $TiCl_2(OTf)_2$: diisopropylethylamine : methyl 3-phenylpropionate=1.3 : 3.0 : 2.0.

(ethoxymethyl)ethyl methyl adipate (21) were attempted, but more fruitful results were not obtaied both in yield and with selectivity (Scheme 4). The use of N,N-diisopropylethylamine (the Hünig base) or N-ethylpiperidine at −23 °C gave the best results in yield and with selectivity as shown in Table 4.

Before the investigation of intermolecular condensation, the temperature to control the undesirable self condensation of methyl esters was fixed using methyl 3-phenylpropionate as a substrate , and −23 °C was found sufficient to the purpose (Table 5). Intermolecular condensations between a variety of methyl esters and methoxymethyl esters were examined under the optimum conditions found for the intramolecular reactions (Table 6). As controlled experiments, commonly employed bases such as potassium hydride (Entry 4) and sodium methoxide (Entry 5) were examined in the same reaction,[13] however, the condensation products were obtained in poor yield with low selectivity.
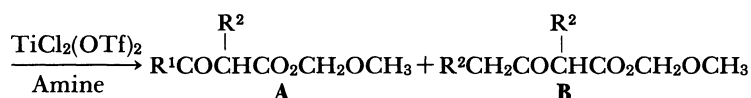
It is notable that the present method could be successfully applied to esters containing base-sensitive functional groups such as α, β-unsaturated, α-chloro, and β-siloxy esters as substrates giving the β-keto esters without the loss of their functionalities (Entries 1, 2, 9, and 10).

In summary, the present method provides the first example of the crossed type-Claisen ester condensation between two different esters (methyl ester and methoxymethyl ester) under mild acidic conditions, and that the resulting methoxymethyl esters of β-keto acids could have wider applicability in organic syntheses.

Experimental

All the melting points and the boiling points are uncorrected. The IR spectra were determined on a Hitachi Model 260-30 spectrometer. The ^1H NMR spectra were recorded with a Hitachi R-24B and a JEOL FX-90Q spectrometers with tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded with a Hitachi R-20B spectrometer. MS and HRMS spectra were obtained with a Hitachi GC/MS M-80 instrument. Purification of products was performed by distillation or column chromatography on silica gel (Wakogel C-200 or Merck, Art. 7734), preparative TLC on silica gel (Wakogel B-5F or Merck Art. 11798).

Preparation of Dichlorobis(trifluoromethanesulfonato)-titanium(IV) (=Dichlorobis(triflato)titanium(IV)). A modified procedure of the reported method[4a] for large scale preparation: To a stirred solution of trifluoromethanesulfonic acid (35.6 g, 0.237 mol) was added titanium(IV) chloride (5.0 g, 0.026 mol) at −50 °C with stirring under an argon atmosphere. The reaction mixture was allowed to warm to room temperature during 3 h with stirring (HCl gas was evolved). Then, sulfuryl chloride (25 ml) was

Table 6. Intermolecular Ester Condensation between Methyl Ester and
Methoxymethyl Ester[a]

$$R^1CO_2CH_3 + R^2CH_2CO_2CH_2OCH_3$$

$$\xrightarrow[\text{Amine}]{TiCl_2(OTf)_2} R^1CO\overset{R^2}{\underset{}{C}}HCO_2CH_2OCH_3 + R^2CH_2CO\overset{R^2}{\underset{}{C}}HCO_2CH_2OCH_3$$

A   B

Entry	R¹	R²	Base	Yield of A/%		Yield of B/%	
1	PhCH=CH	Et	C[b]	82	24	5	25
2	PhCH=CH	Et	D[c]	76	24	8	25
3	$PhCH_2CH_2$	Et	C	83	26	7	25
4	$PhCH_2CH_2$	Et	KH[d]	18	26	13	25
5	$PhCH_2CH_2$	Et	NaOCH₃[d]	Trace		12	25
6	Et	Pr	C	67	27	8	28
7	s-Bu	Et	C	57	29	Trace	
8	$PhCH_2CH_2$	$BrCH_2CH_2$	C	72	30	15	31
9	$PhCH_2CH_2$	Cl	C	45	32	7	33
10	$PhCH_2CH_2$	$t\text{-Bu(Me)}_2SiOCH_3$	C	66	34	5	

a) The reaction was carried out in CH_2Cl_2 at −23 °C for 3 h and at 0 °C for 1 h and the molar ratio of methyl ester : methoxymethyl ester : $TiCl_2(OTf)_2$: amine=1 : 1 : 1.3 : 3.0. b) C; N,N-diisopropylethylamine. c) D; N-ethylpiperidine. d) Potassium hydride or sodium methoxide was used as a promoter in place of $TiCl_2(OTf)_2$ and amine.

added and filtered the liquid portion under an inert atmosphere. The resultant yellow powder was washed with another sulfuryl chloride (25 ml× 2) and dried up with vacumn to give 9.6 g (89%) of TiCl₂(OTf)₂ as powdered yellow crystals; ^{19}F NMR (hexamethylphosphoric triamide) ϕ=77.5 (6F, s, trichlorofluoromethane as an external standard). The quality was checked by the comparison with hexafluorobenzene as an internal standard.

Preparation of Methyl 3-Hydroxy-2-methyl-3-phenylpropionate (1). To a stirred solution of diisopropylamine (1.11 g, 11 mmol) in THF (20 ml) was added 6.9 ml of BuLi in hexane (1.60 M; 1 M=1 mol dm^{-3}) at 0 °C under an nitrogen atmosphere. After 15 min, the resultant mixture was cooled to −78 °C, and methyl propionate (0.88 g, 10 mmol) in THF (5 ml) was added dropwise, followed by stirring at the same temperature for 30 min. Then, benzaldehyde (1.17 g, 11 mmol) in THF (5 ml) was added dropwise and stirred for 1 h at −78 °C. The reaction mixture was poured onto 1 M HCl aq (20 ml) and extracted with ether (20 ml×2). The combined extracts were washed with water and brine and dried (MgSO₄). Removal of the solvent under reduced pressure and distilled gave 1.33 g (66%) of 1: bp 125 °C (oven temp)/0.60 mmHg (1mmHg=133.3Pa), (lit,$^{14)}$ 100—103 °C/0.50 mmHg); IR (neat) 3300, 1690 cm^{-1}; ^{1}H NMR (CDCl₃) δ=0.90, 1.05 (total 3H, d, d, J=7.0, 6.0 Hz), 2.40—2.90 (1H, m), 3.45, 3.53 (total 3H, s, s), 4.55, 5.85 (total 1H, d, d, J= 9.0, 5.0 Hz). 6.80—7.25 (5H, m).

Intramolecular Condensation of Dimethyl Adipate: A Typical Procedure. To a stirred suspension of TiCl₂(OTf)₂ (415 mg, 0.99 mmol) and Molecular Sieves 4A (1.0 g) in dichloromethane (2.0 ml) was added dimethyl adipate (116 mg, 0.66 mmol) in dichloromethane (0.5 ml) at 0 °C under an argon atmosphere. Then, triethylamine (220 mg, 2.18 mmol) in dichloromethane (1 ml) was added dropwise to the mixture. After being stirred at room temperature for 2 h, the reaction was quenched with phosphate buffer (pH 7.0). The organic phase was separated by Celite filtration and washed with water and dried (Na₂SO₄). Removal of the solvent under reduced pressure and purified with column chromatography using hexane-ethyl acetate (5:1) gave 81 mg (80%) of 2-(methoxycarbonyl)cyclopentanone. IR (neat) 1720, 1750 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.60—2.50 (6H, m), 3.00—3.50 (1H, m), 3.75 (3H, s,).

2-(Methoxycarbonyl)cyclohexanone$^{16)}$ (6): IR (neat) 1700 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.50—2.60 (8H, m), 3.10—3.50 (1H, m), 3.75 (3H, 2).

2-Ethoxycarbonyl-5-methylcyclopentanone$^{17)}$ (7): IR (neat) 1720, 1750 cm^{-1}; ^{1}H NMR (CDCl₃) δ=0.85—1.30 (6H, m), 1.50—2.40 (5H, m), 2.95—3.40 (1H, m), 4.00 (2H, q, J=7.0 Hz).

Intermolecular Ester Condensation. A similar procedure of intramolecular condensation of dimethyl adipate except the following conditions; (1) the mixture of the substrates and acylating reagents were added spontaneously to the suspension of TiCl₂(OTf)₂, (2) the temperature and the reaction time were shown in Table 3.

Methyl 2-Methyl-3-oxovalerate$^{15)}$ (3): IR (neat) 1720 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.00 (3H, t, J=7.0 Hz), 1.25 (3H, d, J=7.0 Hz), 2.45 (2H, q, J=7.0 HZ), 3.55 (1H, q, J=7.0 Hz), 3.80 (3H, s).

Ethyl 2-Methyl-3-oxovalerate$^{16)}$ (4): IR (neat) 1720 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.00 (3H, J=7.0 Hz), 1.15—1.50 (6H, m), 2.45 (2H, q, J=7.0 Hz), 3.55 (1H, q, J=7.0 Hz), 4.25 (2H,

q, J=7.0 Hz).

Methyl 2-Benzyl-5-phenyl-3-oxovalerate (5): IR (neat) 1715, 1740 cm^{-1}; ^{1}H NMR (CDCl₃) δ=2.55—2.75 (4H, m), 3.00 (2H, d, J=8.0 Hz), 3.45 (3H, s), 3.60 (1H, t, J= 8.0 Hz), 6.80—7.10 (10H, m); HRMS, Found: m/z 296.1427. Calcd for C₁₉H₂₀O₃:M, 296.1414.

Methyl 2-Benzyl-3-oxo-3-phenylpropionate (8): IR (neat) 1690, 1720 cm^{-1}; ^{1}H NMR (CDCl₃) δ=3.15 (2H, d, J=7.0 Hz), 3.45 (3H, s), 4.40 (1H, t, J=7.0 Hz), 6.80—7.80 (10 H, m); HRMS, Found: m/z 268.1096. Calcd for C₁₇H₁₆O₃: M, 268.1100.

Methyl 2-Formyl-3-phenylpropionate (9): IR (neat) 1720 cm^{-1}; ^{1}H NMR (CDCl₃) δ=2.90—3.35 (2H, m), 3.45—3.55 (0.3 H, m; methylene), 3.55 (3H, s), 6.80—7.20 (5.7H, m), 9.50 (0.3H, d, J=2.0 Hz; aldehyde), 11.30 (0.7H, d, J=12.0 Hz; enol); HRMS, Found: m/z 191.9951. Calcd for C₁₁H₁₂O₃: M, 191.9942.

Methyl 2-Benzyl-3,4-dioxobutyrate (10): IR (neat) 1720 cm^{-1}; ^{1}H NMR (CDCl₃) δ=2.90—3.35 (2H, m), 3.40—3.55 (1H, m), 3.55 (3H, s), 6.80—7.20 (5H, m), 10.05 (1H, s); HRMS, Found: m/z 220.0720. Calcd for C₁₂H₁₂O₄: M, 220.0735.

2-Benzoyl-γ-butyrolactone (11): Mp 54—56 °C, (lit,$^{18)}$ 57 °C); IR (Nujol) 1680, 1760 cm^{-1}; ^{1}H NMR (CDCl₃) δ=2.10—3.10 (2H, m), 4.10—4.60 (3H, m), 7.10—8.10 (5H, m).

2-Formyl-γ-butyrolactone (12): Mp 72 °C, (lit,$^{19)}$ 72.5—73.5 °C); IR (neat) 1740 cm^{-1}; ^{1}H NMR (CDCl₃) δ=2.20—3.20 (2H, m), 4.20—4.55 (2H, m), 6.80 (1H, d, J=12.0 Hz), 11.50 (1H, d, J=12.0 Hz).

Methoxymethyl Methyl Adipate (13): To a stirred solution of methyl hydrogen adipate (3.20 g, 20 mmol) and triethylamine (2.45 g, 24 mmol) in N,N-dimethylformamide (50 ml) chloromethyl methyl ether (1.93 g, 24 mmol) was added at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was quenched with water and extracted with ether (50 ml×2). The combined extracts were washed with water and brine, dried (Na₂SO₄), and condensed under reduced pressure. The crude product was distilled to give 3.30 g (81 %) of 13. Bp 145 °C (oven temp)/ 0.07 mmHg; IR (neat) 1740, 1140 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.50—1.85 (4H, m), 2.05—2.50 (4H, m), 3.35 (3H, s), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 204.1016. Calcd for C₉H₁₆O₅: M, 204.0999.

Methylthiomethyl Methyl Adipate (14): By a similar procedure of preparation of 13, the reaction of methyl hydrogen adipate (3.20 g, 20 mmol) and chloromethyl methyl sulfide (2.12 g, 22 mmol) gave 3.74 g (85%) of 14. Bp 180 °C (oven temp)/0.1 mmHg; IR (neat) 1740, 1140 cm^{-1}; ^{1}H NMR (CDCl₃) δ= 1.45—1.85 (4H, m), 2.00 (3H, s), 2.10—2.55 (4H, m), 3.55 (3H, s), 4.95 (2H, s); HRMS, Found: m/z 220.0786. Calcd for C₉H₁₆O₄S: M, 220.0771.

2-Methoxylethyl Methyl Adipate (15): By a similar procedure of preparation of 13, the reaction of methyl hydrogen adipate (3.20 g, 20 mmol) and iodoethyl methyl ether (4.09 g, 22 mmol) gave 3.83 g (88%) of 15. Bp 150 °C (oven temp)/0.1 mmHg; IR (neat) 1720, 1120 cm^{-1}; ^{1}H NMR (CDCl₃) δ=1.45—1.90 (4H, m), 2.05—2.55 (4H, m), 3.35 (3H, s), 3.50—3.70 (2H, m), 3.55 (3H, s), 4.20—4.40 (2H, m); HRMS, Found: m/z 218.1141. Calcd for C₁₀H₁₈O₅: M, 218.1156.

The Selective Intramolecular Dieckmann Condensation: A Typical Procedure. To a stirred suspension of TiCl₂-

(OTf)₂ (417 mg, 1.00 mmol) in dichloromethane (2.0 ml) was added N,N-diisopropylethylamine (297 mg, 2.3 mmol) in dichloromethane (1 ml) at −23 °C under an argon atmosphere. Then methoxymethyl methyl adipate **13** (157 mg, 0.77 mmol) in dichloromethane (1.0 ml) was added dropwise to the mixture. After being stirred at −23 °C for 1 h, the reaction was quenched with phosphate buffer (pH 7.0). The organic phase was separated by Celite filtration and washed with water and dried (Na₂SO₄). Removal of the solvent under reduced pressure and purified with thin layer chromatography using hexane–ethyl acetate (3 : 1) gave 110 mg (83%) of methoxymethyl 2-oxocyclopentanecarboxylate **16**, and 4.7 mg (3%) of **13** which was recovered. IR (neat) 1750, 1720, 1140 cm⁻¹; ¹H NMR (CDCl₃) δ=1.90—2.50 (6H, m), 2.90—3.30 (1H, m), 3.35 (3H, s), 5.15 (2H, s); HRMS, Found: m/z 172.0731. Calcd for C₈H₁₂O₄: M, 172.0735.

Methylthiomethyl 2-Oxocyclopentanecarboxylate (17): IR (neat) 1750, 1140 cm⁻¹; ¹H NMR (CDCl₃) δ=1.80—2.50 (6H, m), 2.05 (3H, s), 2.90—3.30 (1H, m), 5.00 (2H, s); HRMS, Found: m/z 188.0880. Calcd for C₈H₁₂O₃S: M, 188.0892.

2-Methoxyethyl 2-Oxocyclopentanecarboxylate (18): IR (neat) 1750, 1140 cm⁻¹; ¹H NMR (CDCl₃) δ=1.90—2.55 (6H, m), 2.90—3.30 (1H, m), 3.55 (3H, s), 3.55—3.70 (2H, m), 4.20—4.45 (2H, m); HRMS, Found: m/z 186.0899. Calcd for C₉H₁₄O₄: M, 186.0892,

Isopropoxymethyl Methyl Adipate (19): By a similar procedure of preparation of **13**, the reaction of methyl hydrogen adipate (3.20 g, 20 mmol) and chloromethyl isopropyl ether (2.60 g, 24 mmol) gave 3.85 g (83%) of **19**. IR (neat) 1740, 1130 cm⁻¹; ¹H NMR (CDCl₃) δ=1.15 (6H, d, J=7.0 Hz), 1.30—1.80 (4H, m), 2.00—2.40 (4H, m), 3.55 (3H, s), 3.60 (1H, m), 5.10 (2H, s); HRMS, Found: m/z 232.1332. Calcd for C₁₁H₂₀O₅: M, 232.1312,

Benzyloxymethyl Methyl Adipate (20): By a similar procedure of preparation of **13**, the reaction of methyl hydrogen adipate (3.20 g, 20 mmol) and chloromethyl benzyl ether (3.75 g, 24 mmol) gave 4.60 g (83%) of **20**. Bp 155—159 °C/0.3 mmHg; IR (neat) 1740, 1130 cm⁻¹; ¹H NMR (CDCl₃) δ=1.30—1.70 (4H, m), 2.00—2.30 (4H, m), 3.50 (3H, s), 4.50 (2H, s), 5.15 (2H, s), 7.00—7.20 (5H, m); HRMS, Found: m/z 280.1330. Calcd for C₁₅H₂₀O₅: M, 280.1312.

1-Ethoxyethyl Methyl Adipate (21): To a stirred solution of methyl hydrogen adipate (3.20 g, 20 mmol) and a catalytic amount of p-toluenesulfonic acid (ca. 20 mg) in ether (40 ml) was added ethyl vinyl ether (1.59 g, 22 mmol) at room temperature. After 1 h the reaction mixture was quenched with saturated NaHCO₃ aq and extracted with ether (50 ml). The extract was washed with water and brine, dried (Na₂SO₄), and condensed under reduced pressure. The crude product was distilled to give 3.11 g (67%) of **21**. Bp 180 °C (oven temp)/0.15 mmHg; IR (neat) 1720 cm⁻¹; ¹H NMR (CDCl₃) δ=1.10 (3H, t, J=7.0 Hz), 1.30 (3H, d, J=7.0 Hz), 1.30—1.65 (4H, m), 2.00—2.45 (4H, m), 3.20—3.60 (2H, m), 3.50 (3H, s), 5.75 (1H, q, J=7.0 Hz); HRMS, Found: m/z 232.1318. Calcd for C₁₁H₂₀O₅: M, 232.1312.

Isopropoxymethyl 2-Oxocyclopentanecarboxylate (22): IR (neat) 1740, 1715, 1140 cm⁻¹; ¹H NMR (CDCl₃) δ=1.50 (6H, d, J=7.0 Hz), 1.90—2.50 (6H, m), 2.90— 3.30 (1H, m), 3.70—4.10 (1H, m), 5.20 (2H, s); HRMS, Found: m/z 200.1052. Calcd for C₁₀H₁₆O₄: M, 200.1049.

Benzyloxymethyl 2-Oxocyclopentanecarboxylate (23): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR (CDCl₃) δ=1.80—2.50 (6H, m), 2.80—3.20 (1H, m), 4.50 (2H, s), 5.25 (2H, s), 7.10—

7.30 (5H, m); HRMS, Found: m/z 248.1044. Calcd for C₁₄H₁₆O₄: M, 248.1049.

Preparation of Methoxymethyl Esters: By a similar procedure of the preparation of **13**.

Methoxymethyl Butyrate: IR (neat) 1730 cm⁻¹; ¹H NMR δ=0.80 (3H, t, J=7.0 Hz), 1.10—1.80 (2H, m), 1.90—2.30 (2H, m), 3.30 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 132.0777. Calcd for C₆H₁₂O₃: M, 132.0786.

Methoxymethyl Valerate: IR (neat) 1730 cm⁻¹; ¹H NMR δ=0.80 (3H, t, J=7.0 Hz), 1.00—2.35 (6H, m), 3.30 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 146.0955. Calcd for C₇H₁₄O₃: M, 146.0943.

Methoxymethyl 4-Bromovalerate: Bp 135 °C (oven temp)/19 mmHg; IR (neat) 1730 cm⁻¹; ¹H NMR δ=1.90—2.70 (4H, m), 3.30 (3H, s), 3.50 (2H, t, J=7.0 Hz), 5.10 (2H, s); HRMS, Found: m/z 209.9881. Calcd for C₇H₁₄BrO₃: M, 209.9891.

Methoxymethyl 2-Chloroacetate: Bp 135 °C (oven temp)/19 mmHg. IR (neat) 1730 cm⁻¹; ¹H NMR δ=3.55 (3H, s), 4.00 (2H, s), 5.25 (3H, s); HRMS, Found: m/z 138.0088. Calcd for C₄H₇ClO₃: M, 138.0084.

Methoxymethyl 3-(t-Butyldimethylsiloxy)propionate: IR (neat) 1715, 1140 cm⁻¹; ¹H NMR δ=0.15 (6H, s), 0.80 (9H, s), 2.55 (2H, t, J=7.0 Hz), 3.60 (2H, t, J=7.0 Hz), 3.30 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 248.1441. Calcd for C₁₁H₂₄O₄Si: M, 248.1444.

The Selective Intermolecular Condensation between Methoxymethyl Ester and Methyl Ester: A similar method of the intramolecular condensation except the point that the mixture of methoxymethyl ester and methyl ester was added.

Methoxymethyl 2-Ethyl-3-oxo-5-phenyl-4-pentenoate (24): IR (neat) 1715, 1140 cm⁻¹; ¹H NMR δ=0.75 (3H, t, J=7.0 Hz), 1.35—2.00 (2H, m), 3.55 (3H, s), 3.70 (1H, t, J=7.0 Hz), 5.15 (2H, s), 6.75 (1H, d, J=16 Hz), 6.90—7.60 (5H, m); HRMS, Found: m/z 262.1222. Calcd for C₁₅H₁₈O₄ : M, 262.1206.

Methoxymethyl 2-Ethyl-3-oxohexanoate (25): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.60—1.00 (3H, t, J=7.0 Hz), 1.05—2.00 (2H, m), 3.15 (1H, t, J=7.0 Hz), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 188.1057. Calcd for C₉H₁₆O₄: M, 188.1049.

Methoxymethyl 2-Ethyl-3-oxo-5-phenylvalerate (26): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.75 (3H, t, J=7.0 Hz), 1.35—2.00 (2H, m), 2.70 (4H, brs), 3.15 (1H, t, J=7.0 Hz), 3.55 (3H, s), 5.10 (2H, s), 6.90—7.30 (5H, m); HRMS, Found: m/z 264.1348. Calcd for C₁₅H₂₀O₄: M, 264.1363.

Methoxymethyl 3-Oxo-2-propylvalerate (27): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.60—1.05 (5H, m), 1.10—1.90 (5H, m), 2.05—2.50 (2H, m), 3.15 (1H, t, J= 7.0 Hz), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 202.1994. Calcd for C₁₀H₁₈O₄: M, 202.1205.

Methoxymethyl 3-Oxo-2-propylheptanoate (28): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.60—1.90 (14H, m), 2.05—2.55 (2H, m), 3.15 (1H, t, J=7.0 Hz), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 230.1496. Calcd for C₁₂H₂₂O₄: M, 230.1519.

Methoxymethyl 2-Ethyl-4-methyl-3-oxohexanoate (29): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.60—1.90 (14H, m), 2.05—2.55 (2H, m), 3.15 (1H, t, J=7.0 Hz), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 230.1505. Calcd for C₁₂H₂₂O₄: M, 230.1519.

Methoxymethyl 2-(2-Bromoethyl)-3-oxo-5-phenylvalerate (30): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=2.10—2.40

(2H, m), 2.70 (4H, brs), 3.15 (1H, t, J=7.0 Hz), 3.55 (3H, s), 3.60—3.85 (2H, m), 5.10 (2H, s), 6.90—7.30 (5H, m); HRMS, Found: m/z 343.0483. Calcd for $C_{15}H_{19}O_4Br$: M, 343.0468.

Methoxymethyl 6-Bromo-2-(2-bromoethyl)-3-oxohexanoate (31): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=1.90—3.90 (11H, m), 3.55 (3H, s), 5.10 (2H, s); HRMS, Found: m/z 358.9508. Calcd for $C_{10}H_{16}O_4Br_2$: M, 358.9494.

Methoxymethyl 2-Chloro-3-oxo-5-phenylvalerate (32): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=2.70 (4H, brs), 3.55 (3H, s), 4.80 (1H, s), 5.15 (2H, s), 6.90—7.30 (5H, m); HRMS, Found: m/z 270.0675. Calcd for $C_{13}H_{15}O_4Cl$: M, 270.0660.

Methoxymethyl 2,4-Dichloro-3-oxobutyrate (33): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=3.55 (3H, s), 4.30 (2H, s), 4.80 (1H, s), 5.15 (2H, s); HRMS, Found: m/z 213.9813. Calcd for $C_6H_8O_4Cl$: M, 213.9801.

Methoxymethyl 2-(t-Butyldimethylsiloxy)-3-oxo-5-phenyl-valerate (34): IR (neat) 1720, 1140 cm⁻¹; ¹H NMR δ=0.15 (6H, s), 0.80 (9H, s), 2.70 (4H, brs), 3.55 (1H, m), 3.20—3.90 (2H, m), 3.55 (3H, s), 5.10 (2H, s), 6.90—7.30 (5H, m); HRMS, Found: m/z 364.2055. Calcd for $C_{20}H_{32}O_4Si$: M, 364.2071.

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